THE CHANGING PATTERN OF PROSTATE CANCER IN NIGERIANS: CURRENT STATUS IN THE SOUTHEASTERN STATES

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This was a ten-year, hospital-based retrospective study for the incidence and clinical pattern of prostate cancer in southeastern Nigeria. Clinical information extracted from the files included the TNM stage, histo-pathological grading, level of prostatic acid phosphatase (PAP), mode of presentation and clinical and biochemical response to intravenous and oral diethylstilboestrol diphosphate (Honvan)/ orchidectomy.

There were 145 patients, mean age 66.6 + 9.8 years, giving an incidence of 61.3 per 10^5, with 54% under 70 years. Most patients (81.4%) presented late, with 62% metastatic. Over 98% were adenocarcinomas, 77% of which were moderate to well-differentiated cancers. PAP was elevated in 109 patients (75%), (representing 92% of all advanced tumours), and normal in 36 (25%). Forty-two percent of poorly differentiated cancers had normal levels of PAP.

Most patients presented with urinary retention (56%), prostatism (44%), anaemia (41%), recurrent UTI (35%), bone pains (20%), haematuria (18%), backache (16%) and paraplegia (6%). Nearly 79% responded to treatment with lowered PAP levels and improved quality of life, within a mean of 26.3 + 13.8 months (range 5-78); objective 81 (58%), subjective 32 (23%), no response 27 (19%). Among paraplegics, 78% had full, and 22% had partial motor recovery. Patients with poorly differentiated cancers had only a 33% two-year survival rate.

This study confirmed an upward, though moderate trend in the incidence of prostate cancer in Nigeria. The use of PAP instead of PSA as the tumor marker, a local diet with high fish content but lower animal fat, and poor hospital access may account for the lower incidence in the southeast. Poor health education may account for the high rate of late presentations. (*J Natl Med Assoc.* 2002;94:619–627.)

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INTRODUCTION

Carcinoma of the prostate gland is arguably the most common malignant tumor among adult men in most western communities.[1,2] It ranks second only to lung cancer as a leading cause of cancer deaths.[3] With the advent of PSA screening programs and increased public

awareness of the disease in the last decade, incidence of prostate cancer in the United States increased by 6% per year,[4] while the corresponding death rate also increased at a rate of 2% to 3% per year.[5] More recently, this incidence has leveled off to approximately 200,000 new cases per year[6] and the accompanying mortality rate also is declining.

Europe has a moderately high incidence, which has increased steadily over the last few years, with Belgium recording an overall increase of 31% over six years.[5] As a racial group, African American men have a higher rate of clinical prostate cancer than their white counterparts of similar education and socio-economic class.[4,7] Ross and co-workers, 1986, reported that blacks in the U.S. have nearly twice the rate of prostate cancer as whites, a situation which is already apparent by the age of 45 years.[8]

In contrast, cancer of the prostate was said to be uncommon among West African blacks, specifically the Nigerian male.[9] Nkposong and Lawani, 1973, also reported that prostate cancer ranked 16th and constituted 2.2% of all malignancies in the cancer registry in Ibadan.[10] Recent reports, however, show that the incidence of prostate cancer is on the rise, and presently ranks among the top ten cancers (or top five of male cancers), in most sub-Saharan African countries, including Nigeria.[11,12] In Nigeria, recent studies have also demonstrated a rising incidence in the southwestern region.[11,13]

Personal observations in recent years in our center gave an impression of an increasing incidence and mortality rate from prostate cancer than was previously observed. This retrospective hospital-based study was, therefore, undertaken to test this observation and to examine the magnitude of such increase, if any. It also was undertaken to establish the incidence of prostate cancer in this hospital, which would serve as a reference point for future studies of the problem in this region of Nigeria, and to compare our findings with those of other studies previously carried out in Nigeria and the West African sub-region. It is hoped that results obtained in this study would be representative of the targeted zone.

PATIENTS AND METHODS

This was a retrospective study, which involved an audit of all patients with histologically confirmed prostate cancer seen in this hospital over ten years (June 1984 to May 1994). The University of Calabar Teaching Hospital (UCTH) is the only major tertiary referral hospital serving the southeast zone of Nigeria, which is made up of two core and several peripheral states. The hospital receives patients from all government hospitals, mission hospitals, and private hospitals and clinics within the zone.

Clinical evaluation of each patient included a general examination with digital rectal examination (DRE), serum prostatic acid phosphatase (PAP), complete blood count, skeletal radiography and chest x-ray. Where the DRE was suggestive, systematic sextant digitally guided trans-rectal needle biopsies were undertaken at a minimum of six sites (three in each lateral lobe), using the Travenol Tru-cut biopsy needle, with intravenous Tobramycin, 80mg to 120mg in a single dose as prophylaxis. The clinical staging of the disease was determined using the TNM system at the time of DRE. The clinical presentation, tumor staging, and histopathological grading were carefully documented and used as the determinants of the tumor behavior and treatment schedule of each patient. TRUS, PSA, and CT scan were not available in UCTH at the time of this study.

After the histopathology report, patients were categorized for androgen ablation in the form of hormone therapy and/or orchiectomy or watchful waiting after a full assessment of their cardiovascular status, taking the age and overall health of the patient into consideration. Patients with severe symptoms, especially under 70 years of age, were treated with high-dose intravenous diethylstilboestrol diphosphate (Honvan) (1.1G), given over ten minutes for ten to fourteen days, followed by a maintenance dose of 140mg tablets three times a day

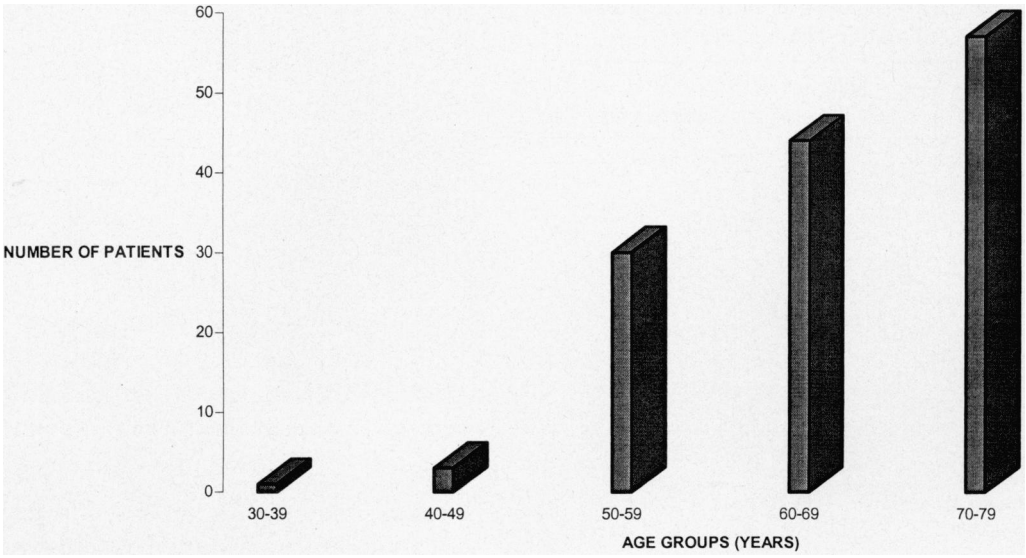

Figure 1. Age distribution of prostate cancer in Calabar, Nigeria.

until relapse or any sign of complication. High dose Honvan was preceded by 10mg intravenous metoclopramide, twenty minutes prior to the injection. Surgical treatment was by total orchiectomy, and by subcapsular orchiectomy in those who objected to complete removal of their testicles, after full counseling and informed consent.

The cases with non-invasive T1 tumors were categorized for watchful waiting; only three patients received any form of radiotherapy by gold grain implants in the U.S., usually after an initial period of endocrine therapy. Each patient was monitored carefully with regular estimations of PAP. A rise of PAP after an initial fall marked tumor recurrence or hormone escape. The time of tumor recurrence (hormone escape) was carefully documented for each patient.

As much as possible, patients were monitored until death; death also was assumed if a patient whose condition had been deteriorating failed to keep his appointment for up to six months. The default rate was estimated to be about 40%, although most returned in the event of a relapse. Results were tested by the student t-test for differences between means.

RESULTS

There were 145 Nigerian patients with confirmed prostate cancer in the ten years under review, giving an incidence of 61.3 per 10^5. This constituted 81% of all urogenital cancers among the male population and 28% of all causes of bladder outlet obstruction seen in this center (unpublished data). The mean age of patients was 66.6 $\pm$ 9.8 years, ranging between 35 and 88 years. The peak incidence was in the age group 60 to 79 years, accounting for 69.7% of all the prostate cancer population, with 54% under 70 years of age. The age group of 50 to 59 years accounted for 30 patients (nearly 21% of all patients). Only 10 patients (7%) were over 80 years of age (see Figure 1).

The mode of presentation of all the patients is shown in Table1. Obstructive uropathy with urinary retention was seen in 81 patients (56%), with 64 patients (44%) presenting with irritative prostatic symptoms only. Anaemia with haemoglobin less than 10G/dl was found in 60 patients (41%); 24 of these (40%) had intractable anaemia with haemoglobin levels of 4 to 5.5G/dl. Persistent/recurrent UTI was the mode of presentation in 51 patients (35%), while 29 patients (20%) presented with bone

Table 1. Clinical Presentation of Prostate Cancer in Calabar, Nigeria

Symptoms	Number of Patients	Percentage (%)
Obstructive Uropathy with Retention	81	56.0
Prostatism without Retention	64	44.0
Anemia	60	41.0
Persistent/Recurrent UTI	51	35.0
Bone Pains	29	20.0
Hematuria	26	18.0
Pedal edema	24	17.0
Intractable Back Pain	23	16.0
Hydronephrosis	12	8.2
Paraplegia	9	6.0
Incidental	6	4.0

pains. Twenty-three patients (16%) presented with intractable backache. Nine of these were paraplegic (6.2%).

Of the 145 patients in the series, 118 (81.4%) presented with late stage disease while only 21 patients (14.5%) were considered to have early stage disease. Six of the 145 patients (4.1%) had no TNM staging in their records (see Table2). Adenocarcinoma was found in 143 of the 145 patients (98.6%); two patients (1.4%) presented with squamous cell carcinoma. One of the latter two patients with squamous cell carcinoma presented with malignant stricture of the prostatic urethra and tumor implantation in the skin at the site of the suprapubic cystostomy performed at the referring hospital (see Figure 2). It is possible that this could have been a case of cancer of the

Table 2. Clinical Stages of Prostate Cancer in Calabar, Nigeria

Clinical Stages (TNM)	Number of Patients	Percentage (%)
T1	8	5.5
T2	13	9.0
T3	28	19.3
T4	90	62.1
Not Stated	6	4.1

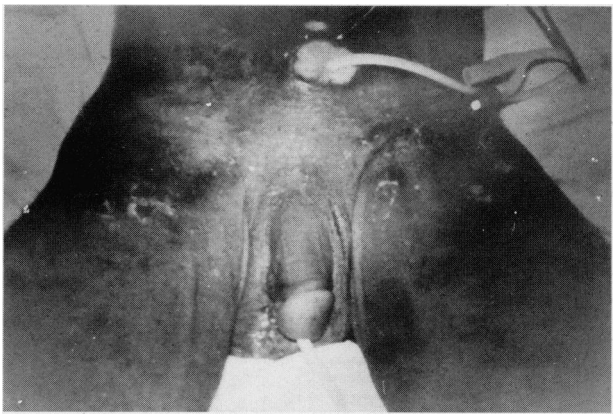

Figure 2. Tumor Implantation Along Cystostomy Tract.

prostatic urethra. There was, however, no historical or clinical evidence of schistosomiasis or bladder cancer in the two patients with sqamous cell carcinoma. Of the 143 adenocarcinomas, 87 (60.8%) were well differentiated, 25 (17.5%) moderately differentiated, and 31 (21.7%) were poorly differentiated. The two cases with squamous cell carcinoma (SCC) had well-differentiated histology.

Serum prostatic acid phosphatase (PAP) was elevated in 109 of the 145 patients (75.2%) and normal in 36 (24.8%). The number of patients with elevated PAP represented 92% of the 118 patients with advanced tumors. Of the 36 patients with normal levels of PAP, 21 (58.3%) had early stage tumors, while 15 (41.7%) had advanced tumors. Thirteen of the 36 patients (36%) with normal levels of PAP had poorly differentiated histology; two were well-differentiated squamous cell carcinomas.

One hundred and thirty nine patients received primary treatment, including three in the T1 category with cancers whose histology showed perineural invasion. The remaining six patients in this category were managed by watchful waiting. One of the six patients with a T1 tumor under watchful waiting had disease progression within two years and was eventually included in the treatment group. This group totaled 140 patients who received primary hormonal treatment and/or orchiectomy.

Following hormonal treatment and/or or-

chiectomy, 110 of the remaining 140 patients (78.6%) became symptom-free for a mean period of 26.3 ± 13.8 months before developing hormone resistance. Only six patients (4.3%) were symptom-free for more than five years, one of these lasting 78 months before a relapse. Ironically, this patient presented with extensive nodal metastasis on initial admission, which all disappeared with Honvan. Five patients developed signs of congestive heart failure during treatment and were taken off the drugs. All of them had orchiectomy as part of their initial treatment. Four patients with T1 tumors remained free of symptoms for six years before they stopped attending for checks. One was lost to follow up after two years attendance.

During injections, patients with metastases usually experienced varied intensities of "burning and itching sensations" and pains in the anogenital region and at sites of secondaries, especially along the spines, ribs and other bones. This observation was so consistent that we could predict from it the extent of disease in a patient. Eighty-one of 140 patients (58%) had measurable objective response to therapy as measured by tumor shrinkage and PAP levels, many of whose prostatic beds became flat on DRE (57 complete, and 24 partial). In most of these, the PAP fell to castrate levels. In 32 patients (23%), response was only subjective with only slight to moderate changes in the DRE findings, although the patients' quality of life improved. In 27 (19%), there was no response at all. On average, the period between relapse and death was 4 to 13 months. Most patients with poorly differentiated cancers responded poorly to hormonal treatment, with a two-year survival rate of 33%. No patient in this group survived for five years. Only three patients in the series (2.1%) had radiotherapy by gold grain implant in the U.S., having started earlier with hormone therapy. One survived for five years, while the other two lived for 37 and 43 months, respectively. About 40% of the patients defaulted while they were in remission. Those who had not succumbed to their diseases always returned during relapse.

Nine patients presented with paraplegia as a result of spinal cord compression by the tumor. All responded dramatically to therapy with high dose intravenous diethylstilboestrol diphosphate (Honvan). Response was usually evident within days to a week. All patients experienced varied intensities of nausea and sometimes, vomiting. Seven patients had full motor recovery (77.8%), while two (22.2%) obtained grade three muscle power from initial flaccid responses. The quality of life of these patients in remission was very impressive. Most of the responders returned to normal daily activities within weeks. Pedal oedema in all 24 patients who presented with this cleared within two weeks. Response of pain to Honvan was usually evident within days and bone pains and backache usually disappeared within seven to 14 days.

DISCUSSION

Earlier studies in the West African sub-region showed that prostate cancer, like other cancers, was an uncommon disease among West African blacks.[9,10] Health care workers from other parts of Africa also expressed similar views.[14] This pattern appears to be changing. Recent studies in East, West and Southern Africa have indicated a rising trend among black Africans, in contrast to earlier observations.[9,10,13–15] Prostate cancer also has emerged as the most common male cancer in the records of the Ibadan Cancer Registry.

Relative ratio frequency of prostate cancer among all cancers has shown a steady increase over the last two to three decades, rising from 2.2% in 1973 to 11% by 1996.[10,11] A recent study from Lagos, in southwestern Nigeria by Osegbe, 1997, obtained an incidence of 127 per 10^5, a figure which is reportedly comparable to the incidence among African Americans who have the highest incidence in the world.[1,13] Another report from a recent survey in Western Nigeria also shows that prostate cancer now accounts for 16% of all cancers, topping the list of all male cancers (Osifo, B & Shittu, OB, 2001—personal communication).

There were 145 confirmed clinical prostate cancer patients in this study. With an incidence of 61.3 per 10^5, our results show a moderate but definite increase in the incidence of prostate cancer over previous unpublished observations in this center and those from other studies in the West African sub-region.[9,10] Prostate cancer also is definitely causing more deaths than was previously noted. This result confirms current observations in various parts of the African continent.[11,13–15] In addition, it shows that there probably is a geographic variation in the epidemiology of prostate cancer within Nigeria,[15,16] although this assertion cannot be tested at this stage of the study.

Although the clinical incidence obtained in this study indicates a moderate rise in trend, it is conceivable that our figure underestimates the true incidence of prostate cancer in our region of Nigeria. The reason for the relatively lower incidence in this study is not yet fully apparent. Dietary animal fat, however, is a known risk factor in prostate cancer. The local diet of the area covered by this study is high in seafood and vegetables and is relatively lower in animal fat than that of southwestern Nigeria. It has been suggested that high fish consumption could be associated with reduced risk of prostate cancer.[17]

If the lower incidence of prostate cancer in our region is confirmed, it may be related, in part, to these dietary differences. Also, the demographic pattern is different; the population is more rural and riverine than the more largely metropolitan populations of the southwest. People in very remote parts do not have easy access to hospitals. The level of poverty among these rural dwellers also may determine their choice of alternative health practitioners for their health needs, hence the distorted statistics observed. Besides, this study covered a more limited population (less than 10 million) than other studies of the southwest.

The fact that this is a pioneer study in this region also may be a factor for the relatively lower incidence. In addition, the number of trained urologists in the zone is very inadequate. Thus, the observed difference may be an artifact rather than a true geographic variation in the epidemiology of prostate cancer within Nigeria[15,17] as earlier suggested, although this assertion cannot be tested at this stage of the study.

Age is an important risk factor in prostate cancer. The median age of our patients was 66.5 years, with a mean of 66.6 $\pm$ 9.8 years. In the Ibadan study, a mean age of 71.4 years (variance 14.3) was obtained.[11] The difference between these mean ages is, statistically, highly significant ($P < 0.001$), implying that our patients were significantly younger than those in the Ibadan study; 54% being under 70 years of age. The age group of 30 to 59 years accounted for more than 23% of all cases, with 21% being in the age group of 50 to 59 years. A younger age at presentation has been associated with a familial tendency for prostate cancer.[18] This study was unable to confirm or refute this observation, as it was a retrospective study in what might be regarded as virgin territory. Normally, only a few prostate cancers are considered to have a genetic predisposition and this is usually associated with early-onset of the disease.[11] Whether or not this has played any role in this region is a subject for further studies.

It is instructive to note that higher mean testosterone levels have been shown to be important in the aetiology of prostate cancer. Ross et al., 1986, demonstrated higher mean testosterone levels in young blacks in the U.S. by as much as 19% over their white counterparts. Such racial differences have been shown to be enough to account for a two-fold difference in prostate cancer risk among blacks.[8] Since American blacks are of the same racial origin as their African counterparts, it is reasonable to assume that the young black men living in Africa are exposed to the same genetic risks. This may account in part for the observed rising incidence of prostate cancer among black Africans and perhaps, for the younger age incidence observed in this study. However, this information must be tested against the observation in an unrelated study in this center,

in which as much as 33% of a population of infertile men were found to have low levels of testosterone (unpublished observations).

Prostate cancer has a propensity for late presentation. In this study, 81.4% of all of our patients presented with advanced disease, with 62% metastatic at the time of presentation. This finding paints a worse picture than the situation in southwestern Nigeria, where a recent study found that at least 50% of patients presented with advanced stages of neoplastic disease (Osifo B & Shittu OB, 2001: personal information). The observation of these authors is similar to the experience among African American men, 47% of who had advanced disease on presentation, 34% being metastatic disease.[19–23] One-third to two-thirds of patients have been known to have local extracapsular extension or distant metastases at the time of diagnosis.[24] This contrasts sharply with the experience among American whites, 33% of whom had advanced disease on presentation, with 20% metastatic.

More recent studies in the U.S. indicate that the rate of node metastasis has dropped sharply to between 5% and 7%.[22,23] This indicates that patients are being diagnosed earlier because of regular medical checkups using PSA, implying earlier detection in contrast to the situation in Nigeria.

Only a dismal 14.5% of our patients presented with early stage disease. This compares with 67% among white American men and 53% among African Americans. This finding is indicative of the extent of failure of public education efforts or its non-availability in our region. It may also be an indication of the poor penetration of health care facilities in the community.

This study was fraught with limitations, which may have affected our staging and the overall results. DRE and PAP were relied upon for the detection of disease in this study. With a sensitivity of only 52% to 68%, DRE is associated with low detection of early disease when used alone.[24] It is also subject to both overstaging and understaging when correlated with pathologic extent of the disease.[25,26] Furthermore, 25-35% of tumors occur in portions of the prostate not accessible to the examining finger.[27,28] Although Figueiredo et al., 1995, asserted that TRUS-guided biopsies showed no advantage over digitally guided biopsies, provided that a minimum of nine biopsy cores are taken from the same prostate,[29] reliance on DRE in the absence of CT scan and PSA in this study may have resulted in missing a number of early cases, thus affecting overall results. Despite a specificity of 81%, its predictive value would be greatly enhanced when used in conjunction with these facilities, including TRUS. We usually took a minimum of six cores. Whether or not this made any difference to the predictive value of DRE cannot be ascertained in this study.

The other limitation was the use of PAP in place of PSA as the tumor marker in this study. Because of its poor sensitivity in early disease, it is conceivable that sole reliance on PAP rather than PSA as a tumor marker may have resulted in down staging of some cases, which may, in turn, have contributed to the lower incidence in this study. Elevated values of PAP are, however, directly related to the extent of disease.[30] Abnormal values or values in the upper half of the normal range have more than 80% likelihood of extra-prostatic disease.[31,32] While the use of PSA remains the gold standard for detection and follow-up of prostate cancer, in African and other Third World countries that have very limited health budgets, PAP is likely to remain the only reliable and cheap means for detecting tumor recurrence and monitoring progress for some time to come. Its use in combination with DRE and digitally guided biopsies remain the only means of diagnosis in Africa and much of the developing world. In view of the increasing incidence of this disease in Nigeria, the selective use of PSA in all major centers that treat prostate cancer is advocated. This is expected to bring diagnostic protocols in line with the standard practice in other parts of the world, thus making results comparable.

In conclusion, this study has confirmed an

upward trend in the incidence of prostate cancer in the southeast, agreeing with observations elsewhere in Nigeria. The rate of increase in the southeast is currently less than that observed in the southwest. This observation may have grossly underestimated the true incidence, in that the PAP and DRE have been relied upon as diagnostic tools in place of PSA, TRUS and CT scan. In the Ibadan study, PSA was used as the tumor marker. This may have contributed to more cases being detected earlier. Conversely, the observed lower incidence in this study may be real, reflecting on the high seafood content of the local diet, which is particularly rich in fish and vegetables and lower in animal fat.

The largely rural population, poor access to orthodox medical facilities, paucity of urological expertise and greater patronage of alternative medical practitioners in remote areas, are other factors that may also have contributed to the lower rate by diverting patients from the major center of treatment where proper diagnosis and documentation might have been undertaken. Furthermore, patronage of alternative health practitioners may account for the high rate of late presentation observed in this study. Our patients also were significantly younger. For an improvement in our figures, sustained health education aimed at creating a greater awareness of the disease and emphasizing the need for regular medical checks for men aged 50 years and older is advocated nationwide.

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